Beyond the Boxed Warning:

A Call for Regulation of Psychiatry's Most Teratogenic Drug

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The risks of valproate use in pregnancy are extensive and well-established. Its teratogenic effects were first reported in the 1980s, leading to the first boxed warning in 2003.[1,2] The nature of the teratogenicity encompasses a spectrum of congenital malformations, including skeletal, cardiovascular, genitourinary malformations, neural tube defects of varying degrees of severity, and facial deformities such as cleft lip/palate, affecting approximately 11% of exposed fetuses.[3–5]

Additionally, a wide range of neurodevelopmental conditions, including intellectual, cognitive, language, and motor delays; autism spectrum disorder; and attention-deficit/hyperactivity disorder, affect 30–40% of those exposed to valproate in utero.[6–9] These outcomes, collectively known as "fetal valproate syndrome" or "fetal valproate spectrum disorder," are associated with significant disability and are at times incompatible with life, making valproate the most serious teratogen in psychopharmacology.[10–12]

In the United States, approximately 45% of pregnancies are unplanned,[13] and people with mental illness demonstrate a greater likelihood of unintended pregnancies than the general population.[14–16] Unintended pregnancies will typically be recognized beyond the timeframe of neural-structural development, a time of vulnerability to teratogenicity from in utero exposure to valproate.[17] Furthermore, once a pregnancy is recognized, a woman taking valproate faces the difficult decision of whether to terminate the pregnancy—and if continuing the pregnancy, whether to discontinue valproate treatment and risk relapse of mental illness.

Warnings of the risks of valproate in pregnancy have been issued by domestic and international regulatory agencies for over a decade.[18–20] The most recent US Food and Drug Administration (FDA) boxed warning for valproate states, "Valproate should not be administered to a woman of childbearing potential unless other medications have failed to provide adequate symptom control or are otherwise unacceptable" and that women "should use effective contraception while using valproate" and "should be counseled regularly regarding the relative risks and benefits of valproate use during pregnancy."[21] Going further, a recent call was made for providers considering prescribing valproate to women of reproductive potential to simply "forget it exists."[22]

Despite the FDA warning and clear guidance for prescribers, the rate of valproate prescriptions in the US for nonepileptic patients of reproductive age has not declined,[23] nor has the rate of valproate-exposed pregnancies in the last 15 years.[24] When broken down by indication for valproate use in pregnancy, psychiatry predominates, with 52% of prescriptions for mood disorders, 18% for migraines, and 12% for epilepsy.[24] While high-dose folic acid supplementation prior to conception and during pregnancy is routinely recommended for those taking valproate, data have failed to confirm its ability to mitigate the risks.[25]

Several European regulatory agencies have implemented risk minimization measures, which have resulted in reduced valproate exposures in pregnancy.[26–29] Some of these strategies include mandated enrollment in a pregnancy prevention program that encompasses documentation of effective contraception and monthly pregnancy tests, a visual warning displayed on medication packaging, and mandatory annual completion of a form justifying continued use of valproate rather than alternative agents.[12,26,30,31] The US FDA has enacted Risk Evaluation and Mitigation Strategies (REMS) for medications with teratogenic risks similar to valproate.[32] For example, the iPLEDGE REMS system for isotretinoin, an acne medication with high potential for teratogenicity, requires that patients using the medication (1) attest to either abstinence or use of two simultaneous and continuous forms of contraception, (2) provide written acknowledgment of the teratogenic risks, and (3) undergo pregnancy testing prior to treatment and monthly during treatment.[33]

Clearly, safeguards should be in place in the US. We propose creating a REMS for monitoring of valproate prescription to women of reproductive age. This valproate REMS could include the following measures:

1. Signed patient consent indicating the reason for valproate use and acknowledgment of teratogenic risk.
2. Patient receipt of contraceptive education and a pregnancy prevention guide (similar to iPLEDGE for isotretinoin).
3. Confirmation of a reliable contraception method or confirmation of changes incompatible with pregnancy (eg, hysterectomy or menopausal state).
4. For patients capable of pregnancy, reliable documentation of nonpregnancy prior to valproate initiation and at every psychiatric outpatient visit during the course of valproate treatment.

Furthermore, we recommend addition of visual warnings of teratogenicity to valproate packaging.

In conclusion, while valproate remains an invaluable medication for certain severe psychiatric and neurologic health conditions,[34] the high risk of teratogenicity necessitates stringent safeguards to regulate its use by individuals capable of pregnancy. Current data indicate an alarming persistence of valproate-exposed pregnancies despite existing warnings. A structured REMS program incorporating mandatory patient consent, robust contraceptive education, periodic verification of pregnancy status, and clear labeling could significantly mitigate these risks. By aligning efforts with successful European strategies and similar FDA regulations for other teratogenic drugs, we can ensure that the therapeutic benefits of valproate are harnessed while safeguarding against preventable fetal harm. Implementing these measures is imperative to uphold patient safety and public health.

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